Canad. Med. Ass. J.
Oct. 28, 1967, vol. 97

We hope that in time we will be able to provide metabolic screening tests for all newborn infants in this region.

Recent progress in pediatrics and the understanding of the exact pathogenesis of this newly discovered inborn error of metabolism should permit us not only to make an early diagnosis, but also to treat this disorder efficiently. Although at this time we cannot reach definite conclusions, we hope that, with diet, children with this disease may be able to have the same advantages of treatment as those suffering from galactosemia and phenylketonuria.

ADDENDUM

We regret to report that the two patients who were on the diet died recently. The first one died at seven months with all the symptoms of a bulbar encephalitis. There was diffuse hepatic fibrosis, but no nodular cirrhosis. The second infant died at 3 months, soon after signs of hepatic insufficiency appeared. The liver, the pancreas and the kidneys all showed the changes associated with this disease.

While on the diet, these two patients were asymptomic and the laboratory tests remained normal until their deaths. Two additional patients are progressing normally with the diet. Seven other patients died almost immediately after being admitted to hospital.

Pathological Findings in Patients with Tyrosinemia

L. PRIVE, *Chicoutimi, Que.*

LIVER tissue was studied in 29 of the 37 infants from the Chicoutimi area described by Dr. Larochelle and his colleagues. Complete postmortem examination was carried out in 25 and liver biopsies in the four others. Except for generalized edema and signs of diffuse hemorrhage, the abnormal autopsy findings were usually limited to the liver and kidneys.

Grossly, the liver was slightly to moderately enlarged, rather yellowish, firmer than normal, and very faintly nodular. A variable number of small pale spots were discernible through the capsule and on the cut surfaces. The kidneys were enlarged, sometimes up to three times the normal weight. They were pale, soft and edematous, with poor architectural demarcations (Fig. 5).

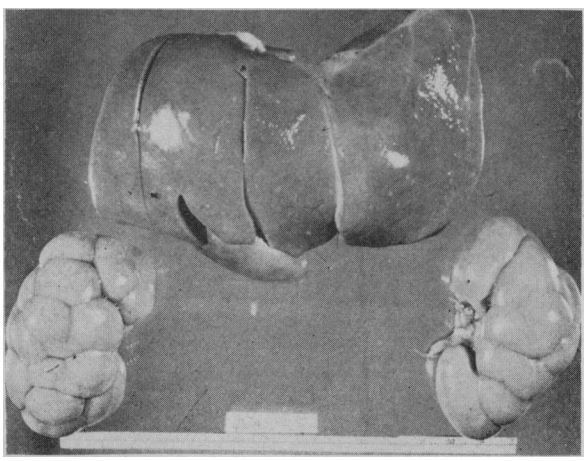

Fig. 5.—Gross aspect of liver and kidneys.

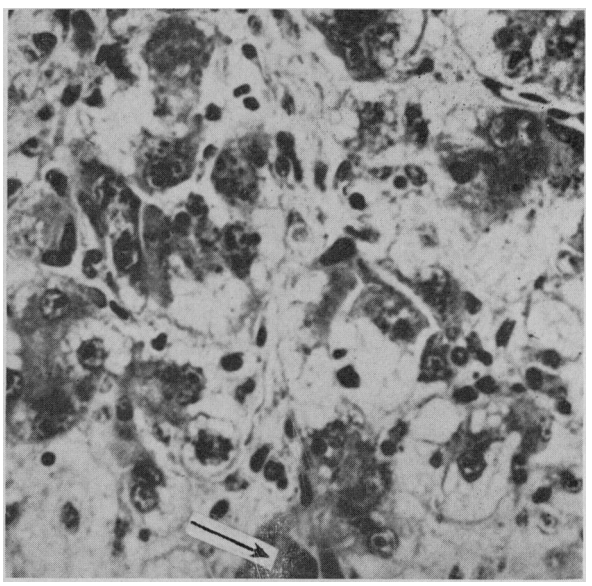

Fig. 6.—Liver: vacuolar degeneration of liver cells and infiltration, chiefly with monocytic inflammatory cells. Bile lake is visible at the bottom of the photograph. (× 400.)

Microscopically, the liver showed a diffuse and loose fibrosis, severely distorting the lobules but not destroying them completely. Associated with this fibrosis was a diffuse inflammatory infiltrate mostly composed of lymphocytes and monocytic cells. There was bile stasis, as evidenced by intralobular bile lakes. A great number of liver cells showed pyknosis and incomplete degeneration (Fig. 6). The cytoplasm of these cells contained numerous vacuoles, which on special staining proved to be fatty material. Histo-

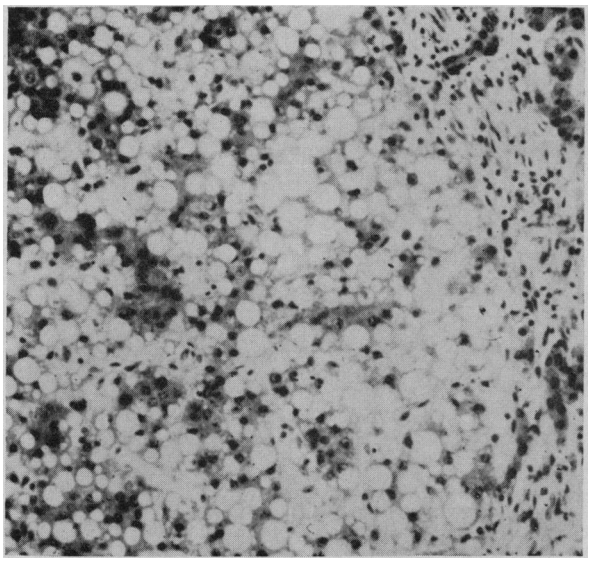

Fig. 7.—Liver: a nodule of regeneration with fatty metamorphosis. (× 250.)

logically, the paler yellowish foci, noted macroscopically, were nodules of intense fatty metamorphosis without fibrosis, which we interpreted as early nodular regeneration (Fig. 7).

Microscopical sections of the kidneys revealed interstitial edema and marked dilation of the tubules. The epithelium of the latter often showed slight to moderate finely vacuolar and granular degeneration. In some cases there were also granular casts and a few foci of calcium deposits. The pathological specimens in all cases, including liver biopsies, showed similar changes. The photographs have been sampled at random.

Compared with other cases already described in the literature, these infants seemed to have more acute liver damage, as evidenced by cell degeneration, young and loose fibrosis and much less nodular regeneration. However, the process could still be the same because in our series the disease affected young babies and was fatal within days or a few weeks at the most.

We also have reviewed our material for hyperplasia of the islets of Langerhans and have found unquestionable islet hyperplasia in over 50% of these infants. In the remainder, there was slight or dubious hyperplasia.

DISCUSSION

DR. SCRIVER: You had a deficit of boys in the study; were there more deaths in boys in the early period of life?

DR. LAROCHELLE: No. I think the sex incidence is about the same.

DR. SASS-KORTSAK: Did the young patients in the early stages have abnormal serum proteins?

DR. LAROCHELLE: Yes. In the 3-week-old baby the protein was around 5 g. %, so that it was abnormal.

DR. SILVERBERG: I would like to ask first of all whether the transaminase peaks were never over 60 units, because, in this age group, this would be considered to be relatively normal, although it may depend upon the method that you are using.

DR. LAROCHELLE: It was always around 80.

DR. SILVERBERG: Did you look for glycogen in your liver biopsy?

DR. PRIVÉ: No, we never did glycogen studies.

DR. COX: May I ask whether the two children on the diet who are still living are showing any signs of physical growth, and whether or not you have supplemented the diet with either phenylalanine or tyrosine?

DR. LAROCHELLE: The weight of these children was normal at birth; however, after the beginning of the sickness, they did not gain weight. With the diet, they are gaining weight fast. One of them has gained about 2½ pounds in the last month. So I think the diet is very effective in these two cases.

DR. COX: Did you supplement it at all with any phenylalanine?

DR. LAROCHELLE: Yes, we are now giving it in the milk that we are preparing and we are giving any kind of fruit and vegetable. The blood tyrosine and phenylalanine levels are normal.

DR. SASS-KORTSAK: In our patients we had to keep the phenylalanine intake rather low. We monitored the patients by measuring blood phenylalanine and tyrosine levels. We found that if you go above the amounts of phenylalanine recommended for phenylketonuria, the blood tyrosine level rises. In the patient we had with marked tubular loss of amino acids, we were never able to get the blood phenylalanine levels up to normal, because every time we increased the phenylalanine intake, the Millon-reacting substances increased in the urine too.

DR. KOOH: What were the abnormalities of the platelets? Was the number decreased?

DR. PRIVÉ: The platelets were decreased.

DR. LAROCHELLE: I think the platelets were low because of hypersplenism.

DR. JELIU: In that respect, I can add something. The second patient (P.L.) described by Dr. Scriver is now on the diet. She is receiving 75 mg. of tyrosine per kg. body weight. She is quite all right, but not as satisfactory as we would want. First, her weight is stationary—she has not gained for one whole month; the tyrosine level is normal. Before going on the diet, she had a bout of bleeding; the prothrombin time was prolonged, and the platelet count was 4000 or 8000 per c.mm. The bone marrow was done at this time and was normal. Now,

since the child is on the diet, the platelets are normal, but the prothrombin is still only 25% of normal. Hepatic tests, flocculation tests and transaminase are still abnormal and the child is not gaining weight.

DR. SASS-KORTSAK: How long after the beginning of the diet?

DR. JELIU: I would say around one month now.

DR. SASS-KORTSAK: I think some things respond very quickly and others respond more slowly.

DR. SILVERBERG: I would like to clarify one of the statements made, i.e., that there was a reduced total protein. We had only one early case, and in this patient there was marked hypoalbuminemia, but the gamma globulin was relatively elevated. In the three older patients, the albumins were normal, but the gamma globulin was elevated in one and not in the others. I wonder if Dr. Larochelle fractionated the serum proteins to see what the gamma globulin was in his patients.

DR. LAROCHELLE: The globulin and albumin were low, but their relative values were quite normal. The gamma globulins were elevated in about six or seven patients only.

DR. FRASER: I have a short question for Dr. Privé. In two patients we saw some anatomical abnormalities of the kidney; we had a horseshoe kidney and a bifid kidney, and the reason I was prompted to ask this question was that you showed fetal lobulation. None of these things is specifically abnormal if you see them once or twice, but did you see a high incidence of any of these features?

DR. PRIVÉ: I don't think so. They were all normal.

Clinical and Biochemical Study of Three Patients with Tyrosyluria

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THREE patients with tyrosyluria were observed. This communication reports the clinical manifestations. A detailed study of the secondary metabolic derangements, and observations on the effect of treatment with a diet low in tyrosine and phenylalanine, appear in a later section of this Conference.

One of the patients was referred to us by Dr. Maurice Tremblay of Chicoutimi, Quebec. The other two (E.R. and C.R.) were a brother and sister from the Toronto area, children of Anglo-Saxon descent.

The main clinical characteristics and the course of these patients are summarized in Table VII. Two were male and one was female. Two siblings of B.H., one older and one younger, are both well. The parents of these patients are not known to be related; however, the parents of B.H. are from families who lived, as far back as they can be traced, in the Chicoutimi area and therefore may have common ancestors. All four parents are healthy. There was nothing remarkable about the pregnancies. All three patients were born after normal labour and were of normal birth weight. The newborn period was unremarkable.

TABLE VII.—SUMMARY OF CLINICAL FINDINGS AND COURSE

	B.H.	*E.R.*	*C.R.*
Sex	M	M	F
Family history	2 siblings well	1 affected sibling	1 affected sibling
Parental consanguinity	—?	—	—
Pregnancy	Normal full-term	Normal full-term	Normal full-term
Birth weight (kg.)	4.17	3.40	3.35
Age at onset (months)	3	5	4
Presentation		Failure to thrive	
Manifestations:			
Cirrhosis	+	+	+
Rickets	±	+	+
Renal tubular defect	+	+	+
Hemolytic anemia	+	±	+
Hypoglycemia	+	+	+
Mental defect	—	±	—
Age at death (years)	1½	4	9/12
Cause of death	*E. coli* sepsis	Hepatoma	Liver failure

In each, the mode of presentation was failure to thrive between 3 and 5 months of age. All three had rapidly progressive cirrhosis of the liver. The R. siblings had definite rickets; B.H. had only mild and transient rickets. All had evidence of renal tubular defect. Two patients had chronic low-grade hemolytic anemia. All three had fasting hypoglycemia of moderate to marked degree. There were no signs of mental defect in B.H. and C.R. The patient who lived the longest (E.R.) eventually had a slight lag in his intellectual development. Whether this was secondary to chronic debilitating disease or was a specific part of this condition is difficult to determine.

Supported by a grant from the Medical Research Council of Canada. Much of this investigation was carried out in the Clinical Investigation Unit of The Hospital for Sick Children, which is supported by the Medical Research Council and the Trustees of the hospital.